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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/656,192
Filing Date: September 08, 2003
Appellant(s): COOPER ET AL.

Sarah Kagan
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5/27/2009 and 7/15/2009 appealing from the Office action mailed 10/27/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference characters and (2) for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function

and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters.

The brief is deficient because the summary of claims 1, 8, 17, 26 and 28 indicates that the claims encompass both a product and a method. To be very clear, claims 1, 8, 17, 26 and 28 are product-by-process claims.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: Claims 1-2, 8-9, 11-12, 17-18, 26, 28, 30, 34, 38 and 103 are rejected under 35 U.S.C. 102(b) as being anticipated by Hanson et al. (US Patent 5,844,107).

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejection of claims 53, 65 and 78 under 35 U.S.C. 102(b) as being anticipated by Hanson et al. (US Patent 5,844,107).

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,844,107	HANSON	1-1995
6,177,274	PARK	1-2003

Schacht et al. *Delivery of Nucleic Acid Material to Target Cells in Biological Systems*, WO98/19710 (14 May 1998).

Mao et al., *Chitosan-DNA nanoparticles as gene carriers: synthesis, characterization and transfection efficiency.* Journal of Controlled Release, vol.70, pp.399-421 (2001).

Kwoh et al., *Stabilization of poly-L-lysine/DNA polyplexes for in vivo gene delivery to the liver.* Biochimica et Biophysica Acta 1444 (1999), pp.171-190.

Martin et al., *Observation of DNA-polymer condensate formation in real time at a molecular level*. FEBS Letters 480: 106-112 (2000).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 8-9, 11-12, 17-18, 26, 28, 30, 34, 38 and 103 are rejected under 35 U.S.C. 102(b) as being anticipated by Hanson et al. (US Patent 5,844,107).

Claim 1 is directed to a non-naturally occurring composition comprising a plurality of unaggregated nucleic acid complexes, wherein individual complexes of said plurality consist essentially of a single nucleic acid molecule and one or more polycation molecules, wherein said complexes are formed by mixing said nucleic acid molecule and said polycation molecules, wherein prior to mixing said polycation molecules have a counterion selected from the group consisting of acetate, bicarbonate, and chloride, wherein a subset of said complexes are rod-shaped when visualized by transmission electron microscopy, wherein the rod-shaped complexes have a diameter of 10-20 nm when visualized by transmission electron microscopy, wherein the nucleic acid molecules of the rod-shaped complexes are condensed, and wherein said complexes are colloidally stable in normal saline.

The composition claims of the instant application are product-by process claims. According to MPEP 2113, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). The claimed compositions are anticipated by the compositions of Hanson et al.

Hanson et al, "non-naturally occurring soluble compacted complexes of a nucleic acid and a carrier molecule" (column 66, lines 36-37). Hanson et al. further teach unaggregated nucleic acid complexes having a single nucleic acid molecule and one or more carrier molecule (col. 64, claim 1). Hanson et al. teach DNA/poly-L-lysine complexes, indicating that the carrier molecule is a polycation. The claim limitations require that the complex is formed using a counterion selected from the group consisting of acetate, bicarbonate and chloride. Hanson et al. clearly teaches condensation of DNA-poly-L-lysine complexes using, sodium chloride (col.21, lines 10), thereby anticipating the counterion limitation. The resulting composition comprises a heterogeneous morphology of shapes and sizes of complexes. The instant specification also indicates that a variety of shapes and sizes of complexes can be formed by condensing DNA with polylysine (Spec., page 13, last paragraph to page 14, paragraph 1; and Example 1, pages 15-16). The limitations of the claim also require a diameter of 10-20 nm for the rod-shaped form of the composition. Hanson teach

"electron microscopic results have been indicated as follows: the association of the polycation with the DNA results in…the structure resulting from the condensation are rod-like relaxed toroids of increased size (relaxed)" (col.62, lines 51-54). Hanson et al. further teaches a relaxed complex having "rod-like fibers (usually 10-20 times the diameter of naked DNA fiber, i.e., usually 10-20 nm thick, and longer than 60 nm) of DNA and branched toroidal structures of increasing size" (col. 58, middle of page). Hanson et al. indicates that their compositions are in a colloidal form (col.54, line 8). Hanson et al. indicate that condensed DNA-poly-L-lysine complex remains stable in solution (col.22, line 15).

Claim 2 is directed to the composition of claim 1, wherein the polycation molecules are polylysine or a polylysine derivative. Hanson et al. teach a "preferred polycation is polylysine" (col.16, line 15).

Claim 8 is directed to the same composition as claim 1, except for the further limitations that (1) the nucleic acid molecule encodes at least one functional protein and (2) the polycation has a nucleic acid binding moiety. Hanson et al. teach the DNA expresses a "protein product" (page 17, column 46). Hanson et al. also teach "in some embodiments, a tissue-specific carrier molecule is prepared, which is a bifunctional molecule having a nucleic acid-binding moiety and a target tissue-binding moiety" (col.5, lines 3-7) and "the nucleic acid is still compacted by complexing with a carrier molecule comprising a nucleic acid binding moiety" (col.5, lines 12-14).

Claim 9 is directed to the composition of claim 8, wherein the polycation molecules are polylysine or a polylysine derivative. Hanson et al. teach a "preferred polycation is polylysine" (col.16, line 15).

Claim 11 is directed to the non-naturally occurring composition of claim 8 wherein said nucleic acid molecule comprises a promoter which controls transcription of RNA molecule encoding the functional protein. Hanson et al. teach the limitation of claim 11, "promoter" (17 column, line 41).

Claim 12 is directed to the non-naturally occurring composition of claim 8 wherein the protein is therapeutic. The limitations of claim 12 that the protein product is "therapeutic" are taught by Hanson et al., explicitly listing therapeutic genes, "coagulation factors…enzymes...receptors" (column 16, lines 40-48).

Claim 17 is directed to the same composition as claim 1, except for the further limitations that (1) the nucleic acid molecule is cDNA and (2) the nucleic acid molecule encodes at least one functional protein. Hanson et al. teach the limitation of claim 17, "cDNA" (16 column, line 49). Hanson et al. the DNA expresses a "protein product" (page 17, column 46).

Claim 18 is directed to the composition of claim 17, wherein the polycation molecules are polylysine or a polylysine derivative. Hanson et al. teach a "preferred polycation is polylysine" (col.16, line 15).

Claim 26 is directed to the same composition as claim 1, except for the further limitations that (1) the complexes are described as soluble rather than unaggregated, and (2) the compositions can be made by the process of "mixing a nucleic acid with a

polycation having acetate as a counterion, at a salt concentration sufficient to compaction of the complexes." Hanson et al. teach "non-naturally occurring soluble compacted complexes of a nucleic acid and a carrier molecule" (column 66, lines 36-37). Hanson describes the mixing the condensed DNA-polycation complexes with chaotropic salts, including sodium chloride, ammonium acetate, potassium acetate, and sodium acetate (Hanson, col. 21, lines 47-67). Hanson states "DNA can be compacted to a condensed state by neutralizing its charge, e.g., by addition of a polycation, or otherwise reducing its interactions with solvent, However, the polycation can cause aggregation or precipitation of the DNA if a chaotropic agent is not employed to prevent it. Compaction therefore can be accomplished by judicious use of both the polycation (to condense the DNA) and (as needed) of a chaotropic agent (to prevent aggregation or precipitation)" (col.20, lines 7-15). When a chaotropic salt (e.g., comprising acetate) is mixed with the DNA-polycation complex, acetate becomes a counterion to the polycation. Therefore, the Office concludes that Hanson anticipates acetate as a counterion used in the formation of unaggregated nucleic acid complexes comprising polycations. Accordingly, Hanson teaches the limitations that the compositions can be made by the process of "mixing a nucleic acid with a polycation having acetate as a counterion, at a salt concentration sufficient for compaction of the complexes." Therefore, Hanson teaches Embodiments encompassing the use of chaotropic salts having an acetate counterion and having salt concentrations sufficient to compact the DNA. Furthermore, Hanson et al. teach the composition's structure, as required by the instant claim.

Claim 30 is directed to the composition of claim 26, wherein the polycation molecules are polylysine or a polylysine derivative. Hanson et al. teach a "preferred polycation is polylysine" (col.16, line 15).

Claim 28 is directed to the same composition as claim 1, except for the further limitations that (1) the complexes are described as soluble and without aggregates, (2) (2) the compositions can be made by the process of "mixing a nucleic acid with a polycation having acetate as a counterion, and (3) wherein "said mixing being performed in the absence of added salt." Hanson et al. teach "non-naturally occurring soluble compacted complexes of a nucleic acid and a carrier molecule" (column 66, lines 36-37). The examiner described that Hanson et al. teach the compositions can be made by the process of "mixing a nucleic acid with a polycation having acetate as a counterion," in the discussion of claim 26. However, to fully understand the meaning of "wherein the step of mixing is performed in the absence of added salt," the examiner sought guidance from the Specification. Only one sentence of one paragraph of the specification contains the phrase "absence of added salt:"

> Another aspect of the invention provided here is a method of preparing a composition comprising unaggregated nucleic acid complexes. Each complex consists essentially of a single nucleic acid molecule and one or more polycation molecules. A nucleic acid molecule is mixed with a polycation molecule in a solvent to form a complex. The mixing is performed in the absence of added salt, whereby the nucleic acid forms soluble complexes with the polycation molecule without forming aggregates. Each complex consists essentially of a single nucleic acid molecule and one or more polycation molecules. The complexes have a diameter which is less than double the theoretical minimum diameter of a complex of the single nucleic acid molecule and a sufficient number of polycation molecules to provide a charge ratio of about 1:1, in the form of a condensed sphere, or 30 nm, whichever is larger. The polycation has acetate, bicarbonate, or chloride as a counterion. Optionally, the one or more polycation molecules of the unaggregated nucleic acid complexes are CK15-60P 10, wherein acetate is

> used as the counterion. CK15-60P 10 is a polyamino acid polymer of one N-terminal cysteine and 15-60 lysine residues with a molecule of polyethylene glycol having an average molecular weight of 10 kdal is attached to the cysteine residue. (Page 5, last paragraph, emphasis added by examiner)

Clearly, the product-by-process limitations directed to making such complexes must include some salt, since the polycations, in the cited paragraph, are indicated as having counterions. So the examiner cannot interpret the claims as encompassing a method of condensing the compositions in a mixture devoid of salt. Additionally, the specification does not contain a working example that is totally salt-free, although Hanson does teach making compacted DNA-PLL compositions using a salt-free method (col.53, lines 15-18). The specification provides no guidance as to what scope is encompassed by “mixing is performed in the absence of added salt.” All the specification’s examples use salt when condensing the DNA-lysine complexes. The scope of the claim has not been explicitly limited only to the counterion, acetate. In fact, the open language of the claim permits a reading that encompasses an interpretation (of counterions) as discussed in the rejection of claim 26. Therefore, the examiner concludes that a skilled artisan would broadly interpret the meaning of the scope of "no additional salt.” Accordingly, the Office concludes that Hanson satisfies the limitations of claim 28. Furthermore, the structure of the compositions described in the cited paragraph comprises DNA and polylysine; there is no claim limitation that the composition contains acetate. Hanson et al. teach the structural limitations of the instant claim.

In an alternative claim interpretation, the condensation process could exclude salt in the mixing process, but use chaotropic salts (as counterions) after condensation. Hanson et al. describe some alternative methods in col.23, lines 19-28, in which no salt is used when a carrier molecule comprises a targeting binding moiety (TBM). In such an embodiment, compaction activity of the TBM-carrier molecule requires no salt, but could still require chaotropic acetate salt:

> The preferred minimum initial salt concentration is dependent on the compaction activity of the carrier and the chaotropic activity of the salt. If the NABM were $(Lys)_8$, or $(Lys)_{27}$, the initial NaCl concentration could be zero. With longer polyLys chains, however, in the absence of NaCl, precipitation would be immediate. With $(Lys)_{50}$, the initial NaCl concentration is preferably be at least about 300 mM. Nonetheless, if the TBM is a protein that affects the condensation, the initial salt concentration could be as low as zero.

No matter how the Office interprets the claim, the examiner concludes that Hanson anticipated the claimed composition.

Claim 34 is directed to the composition of claim 28, wherein the polycation molecules are polylysine or a polylysine derivative. Hanson et al. teach a “preferred polycation is polylysine” (col.16, line 15).

Claim 38 is directed to the composition of claim 17, wherein the nucleic acid complexes are associated with a lipid. Hanson et al. teach complexing said unaggregated nucleic acid complexes with lipids (col.65, lines 25-27).

Claim 103 is directed to the composition of claim 8, wherein the nucleic acid complexes are associated with a lipid. Hanson et al. teach complexing said unaggregated nucleic acid complexes with lipids (col.65, lines 25-27).

Accordingly, Hanson et al. anticipated the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Hanson, Park & Schacht

Claims 3, 10, 19, 31, 35, 51-53, 63-65, 67-68, 76-78 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanson et al. (US Patent 5,844,107) in view of Park et al. (US Patent 6,177,274) and Schacht et al. (WO/1998/19710).

Claims 3, 10, 19, 31, 35, 51-53, 63-65, 67-68, 76-78 and 104 are directed to complexes having polylysine of 15-60 residues conjugated to PEG through a cysteine residue.

The teachings of Hanson et al. are described above in the 35 USC 102(b) section. In addition, Hanson et al. teach the limitation of claim 53, 65, 78, "a targeting moiety" in their Abstract, "targeting may be enhanced by means of a target cell-binding moiety." Also, Hanson et al. teach the further limitations of claim 67 "nucleic acid…encodes…functional protein" are taught by Hanson et al. "protein product" (page 17, column 46). Hanson et al. teach the limitation of claim 68 that the protein product is "therapeutic," and have a "therapeutic effect (column 4, line 62), and more explicitly list therapeutic genes, "coagulation factors…enzymes…receptors" (column16, lines 40-48).

Hanson et al. does not teach Polyethylene Glycol (PEG) joined to 15-60 lysine residues (claims 51-52, 63-64) through an N-terminal cysteine linkage (claims 3, 10, 19, 31, 35, 51-52, 63-64) where the PEG has an average molecular weight of 10kD (claims 51-52, 63-64).

Park et al teach incorporation of a PEG of molecular weight 0.5 to 20 kD (column 5, line 29) to the polylysine with the length of 10-250 lysine residues (column 6, line 2-3) through an amino terminal linkage (column 5, line 28).

However, Park et al. do not teach a cysteine moiety that has been incorporated to the N-terminus of the polylysine so as to provide a bridge for attachment to the PEG.

Schacht et al. teach incorporation of a PEG of molecular weights 2kD (page 38, line 19) and 5 kD (page 46, line 14) and 16kD (Figure 4) to the polylysine of molecular mass 4 to 20 kD (intrinsic length of 27 to 137 lysine residues (page 10, line 12) through an amino terminal linkage using a disulfide bond (page 25, lines 22-35).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Hanson et al. with Park et al. further in view of Schacht et al. to link any PEG with MW of 10kD to one or more polycationic agent such as polylysine, having more than at least 15 to 60 residues with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to incorporated any known PEG species to a polycationic moiety contained in the DNA complex of Hanson et al because the concept of utilizing a polycationic polylysine (PLL) linked to PEG whereby PEG-PLL functions as an enhanced linker so as to link the backbone of the PLL to a bioactive molecule or the ligand to a cell of interest (targeting moiety) is well taught by Park. Furthermore, Park teaches that PEG linked to PLL enhances the delivery of a charged therapeutic agent across the bilayer membrane of a target cell.

The person of ordinary skill in the art would have been motivated to make those modifications because both Park and Schacht teach that PEG linked to PLL enhance the delivery of a charged therapeutic agent across the bilayer membrane of a target cell. (Park, column 11, line 46-52 and Schacht, page 2, line 7).

Insofar as the limitation of an incorporation of a reactive group such as a cysteine residue at the N-terminal of a polylysine, which terminal is further linked to a protective hydrophilic polymer such as PEG, the use of any reactive group including the use of a disulfide bond from any well-known source, e.g., cysteine, is also taught in the Schacht reference (page 25, line 22).

It would have been obvious for one of ordinary skill in the art to have further modified the N-terminal of the polylysine by providing a disulfide bridge so as to act as a bridge for PEG's linkage. One of ordinary skill in the art would have been motivated to employ a cysteine, which is well known in the art as a source of disulfide bond used as an attachment point for a reactive group because such use of any reactive group including the use of a disulfide bond from any source is also taught by the Schacht reference.

An artisan would have expected success, because the art of making condensed DNA particles with polylysine is well known.

Therefore the composition as taught by Hanson, Park & Schacht would have been *prima facie* obvious over the composition of the instant application.

Hanson, Park, Schacht & Mao

Claims 58-62, 66, 73-75, 79-82 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanson et al. (US Patent 5,844,107) in view of Park et al. (US Patent 6,177,274) and further in view of Schacht et al. (WO/1998/19710) as applied to claims 3, 10, 19, 31, 35, 37, 51-53, 63-65, 67-68, 76-78 and 104 above, and further in view of Mao et al. (Journal of Controlled Release 70 (2001) 399–421).

Claims 58-62, 66, 73-75, 79-82 and 122 are directed to lyophilized forms of the claimed compositions and to subsequent resuspension of complexes prior to use in methods of treatment of cells.

Claim 61 is directed to a method of delivering polynucleotides to cells comprising: contacting the composition of claim 59 (dependent from claim 51) with cells, whereby the nucleic acid is delivered to and taken up by the cells. Claim 75 is the same as claim 61, except that it uses the composition of claim 73 (dependent from claim 63). Claim 82 is the same as claim 61, except that it uses the composition of claim 80 (dependent from claim 76).

Hanson et al. teach the limitations of claims 61, 75, 82 that "nucleic acid is delivered to and taken up by cells." Hanson et al teach "DNA molecules taken up by each cell." (column 13, lines 21). Park et al further teaches the limitation of claim 61, 75, 82 that "nucleic acid is delivered to and taken up by cells." Park et al teach "composition enters said cells, and the nucleic acid of said composition is released." (column 16, lines 1-4). Also, Hanson et al. teach the further limitations of claims 67, 75, 82, "nucleic acid…encodes…functional protein" are taught by Hanson et al. "protein

product" (page 17, column 46). The limitation of claim 68 that the protein product is "therapeutic" is taught by Hanson et al. "therapeutic effect (column 4, line 62), more explicitly listing therapeutic genes, "coagulation factors…enzymes…receptors" (column16, lines 40-48.

Furthermore, Hanson et al teach the limitation of claims 62, 74, 81, 122 that the delivery method does not use a disaccharide, writing, "one class of ligands…are carbohydrates, especially…oligosaccharides…another class of ligands…are peptides" (column 14, line 26-31). Clearly, embodiments of Hanson which use peptides encompass compositions that do not contain a disaccharide.

The Hanson, Park, and Schacht references do not teach lyophilization of the complex. Park et al. also does not teach the methods of delivery where the composition does not contain a disaccharide (claims 62, 74, 81, and 122).

Mao et al. teach lyophilization of the complex and administration of the complex to cells (page 419). It is clear from the art and context of the reference that the complex is resuspended prior to administration.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to lyophilize the DNA-PEG-polylysine complex and to later resuspend it in order to administer it to cells.

The person of ordinary skill in the art would have been motivated to make that modification to lyophilize and resuspend the instant invention because it is an art established method of preserving gene therapy products (i.e., condensed nucleic acids)

prior to clinical use. An artisan would have expected success, because the art was aware of these techniques and was using them by the time of the instant application.

Therefore the method as taught by Hanson et al. with Park et al. and Schacht et al. and in further view of Mao would have been *prima facie* obvious over the method of the instant claims.

Hanson, Park, Schacht & Kwoh

Claims 4-7, 13-14, 39-40, 54-55, 69-70, 106-107, and 114-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanson et al. (US Patent 5,844,107) in view of Park et al. (US Patent 6,177,274) and further in view of Schacht et al. (WO/1998/19710) as applied to claims 3, 10, 19, 31, 35, 37, 51-53, 63-65, 67-68, 76-78 and 104 above, and further in view Kwoh et al. (Biochimica et Biophysica Acta 1444 (1999) 171-190).

Claims 4-7, 13-14, 39-40, 54-55, 69-70, 106-107, and 114-115 contain limitations directed to transmission electron microscopic characterization of the rod-shaped complexes. In particular, the instant claims contain the limitation that the condensed particles have a rod shape when viewed by electron microscopy and that the rods have a length of 100-300 nm and a diameter of 10-20 nm. Kwoh et al. teach these limitations.

Kwoh et al. teach (poly-L-lysine) "PLLs of all sizes condensed plasmid DNA into toroids and rod-shaped structures…as shown by electron microscopy (page 179,

section 3.4). Figure 4K (page 180) shows a rod-shaped condensed DNA/polylysine complex of greater than 100nm, as determined by scale bar. Figure 4G shows a rod-shaped condensed DNA/polylysine complex of greater than 100nm, as determined by scale bar. Furthermore, Kwoh et al teach that with conjugation of PEG to the PLL-DNA complexes, the sizes of the rods are larger; "rod structures observed in electron micrographs of PLL10K-PEG5K polyplexes were longer and more abundant than rods observed with PLL polyplexes" (page 183). Figure 8B (page 184) show rod-like PLL-PEG-DNA structures in the electron micrographs that are about 200 nm in length, as measured by scale bar. Furthermore, with regard to the limitation of the instant claims that the diameter of the rod-shaped complexes is 10-20 nm, Figure 8D (page 184, center panels) shows a comparison of a PLL-PEG/DNA rod-shaped complex and a small spherical particle 25 nm in diameter (indicated with closed arrowhead)" (page 184). It is clear that the diameter (width) of the rod is slightly smaller than the diameter of the small spherical particle. Although an exact measurement of the diameter (width) of the rod-shaped complexes in the Kwoh et al article are not explicitly described, the sizes are of the rod-shaped complexes shown in electron micrographs fit within the approximate sizes of the instant claims 4-7, 13-14, 39-40, 54-55, 69-70, 106-107, and 114-115. It is clear that at least some of the polylysine-DNA condensed particles fit the length and width of the instant claims. As the claim language is open and the applicant has chosen to only characterize their compositions using limited parameters, the cited art teaches that "a subset of said complexes are rod-shaped when visualized by TEM" and at least a portion of the rod-shaped complexes have a length of 100-200 nm. It

seems to the Office that the claim language allows for a variety of shapes and sizes, but only a portion of them must be 10-20 nm in diameter and 100-200 nm in length.

It would have been obvious for one of ordinary skill in the art to combine the inventions of Hanson et al. and Park et al. and Schacht et al. with the studies of Kwoh et al. in order to characterize the size and shape of the PLL-PEG-DNA complexes using transmission electron microscopy as in Kwoh et al. because it is a standard method employed by those companies and laboratories studying new methods of formulating condensed DNA for non-viral gene therapy. One of ordinary skill in the art would have been motivated to employ electron microscopy to characterize the complexes, because it is well known in the art as method of establishing the size and conformation of the particles.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Hanson et al. and Park et al. and Schacht et al. and Kwoh et al. because the art teaches disulfide linkages were successfully performed between PEG and PLL and characterizing the complexes by electron microscopy has been performed for this purpose many times by many different inventors and researchers.

Therefore the techniques as taught by Hanson et al. in view of Park et al. and Schacht et al. and further in view of Kwoh et al. would have been *prima facie* obvious over the compositions and methods of the instant application.

(10) Response to Argument

Anticipation by Hanson

Appellant's presentation of the teachings (Brief, pages 7-8, section D.1.a):

The appellant asserts that the "Office concedes that Hanson does not explicitly describe the complexes recited" (Brief, page 7, last sentence of parag.2). The appellant uses a footnote (i.e., Final office action at page 4, lines 1-14) to support this assertion. As the appellant has not identified which of the three Final actions made during the application's prosecution history provides support for this allegation, the Office reviewed all of them. There is absolutely nothing in any of the three Final office actions at page 4, lines 1-14, which could be construed as the Office conceding that Hanson does not anticipate the instant invention.

The Office wishes to comment on an assertion of the appellant (Brief, page 8). The appellant characterizes the teachings of Hanson (col.62, lines 51-57) as "Thus Hanson teaches three components in a mixture [aggregate complexes (Aggregated), rod-like relaxed toroids (Relaxed), and toroids (Condensed)]" (Brief, page 8). The citation referred to by the appellant comes from the legend of Table 104, in which Hanson is describing the terminology used in Table 104. At this citation, Hanson is not describing a mixture.

Hanson teach "electron microscopic results have been indicated as follows: the association of the polycation with the DNA results in…the structure resulting from the condensation are rod-like relaxed toroids of increased size (relaxed)" (col.62, lines 51-54). Hanson et al. further teach a relaxed complex having "rod-like fibers (usually 10-20

times the diameter of naked DNA fiber, i.e., usually 10-20 nm thick, and longer than 60 nm) of DNA and branched toroidal structures of increasing size" (col. 58, middle of page). Clearly, Hanson teaches compacted complexes of DNA and polycation, which have a rod shape and are 10-20 nm thick. The Office interprets these teachings as satisfying the structural limitations of the instant claims. Table 104, described in the legend at page 62, lines 51-57, and at col. 23, lines 48, describe the physical state of a variety of DNA-poly-L-lysine compositions formed using a range of different salt concentrations. The purpose of the studies of Hanson was to optimize the compaction of the DNA-polylysine compositions by studying the effect of polycation length and salt concentration on the compaction of DNA-polylysine. Throughout Hanson, there are examples where the concentrations of these variables are varied to produce aggregated complexes or compacted rod-like toroids or condensed toroids. The teachings of Hanson demonstrate examples of unaggregated compacted DNA-polycation complexes having rod-shapes.

Appellant's presentation of the teachings (Brief, pages 8-10, section D.1.b):

The applicant discloses all of the recitations in Hanson of the word, "acetate" (Brief, pages 8-10). Only one of these is relevant to the rejection of the pending rejection. As described in the Brief at page 8, Hanson describes the mixing the condensed DNA-polycation complexes with chaotropic salts, including sodium chloride, ammonium acetate, potassium acetate, or sodium acetate (Hanson, col. 21, lines 47-67). Hanson states "DNA can be compacted to a condensed state by neutralizing its charge, e.g., by addition of a polycation, or otherwise reducing its interactions with

solvent. However, the polycation can cause aggregation or precipitation of the DNA if a chaotropic agent is not employed to prevent it. Compaction therefore can be accomplished by judicious use of both the polycation (to condense the DNA) and (as needed) of a chaotropic agent (to prevent aggregation or precipitation)" (col.20, lines 7-15). When a chaotropic salt (e.g., comprising acetate) is mixed with the DNA-polycation complex, acetate becomes a counterion to the polycation. Therefore, the Office concludes that Hanson anticipates acetate as a counterion used in the formation of unaggregated nucleic acid complexes comprising polycations. Additionally, the Office notes that the structure of the claimed composition comprises DNA and a polycation; the structure of the claimed compositions does not comprise acetate.

Other recitations of the word, "acetate," in Hanson are directed to (1) using uranyl acetate for staining micrographs and not for making DNA-polycation complexes, (2) using sodium acetate to precipitate DNA or proteins during molecular biological techniques and not for making DNA-polycation complexes, and (3) using naphthyl acetate for histological staining and not for making DNA-polycation complexes.

Appellant's presentation of the teachings (Brief, pages 12-15, section E):

The appellant argues Hanson does not inherently teach the same product as claimed because Hanson does not teach the same process of making. The Office is unpersuaded by this argument because MPEP 2113 indicates, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the

same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). The claimed compositions are anticipated by the compositions of Hanson et al., because they have the same structure.

The appellant further argues Hanson teaches other counterions, but not acetate and particularly states that "Hanson teaches polycations such as bromide or chloride" and "Hanson teaches mixing the choride-dialized polycations with nucleic acids" (Brief, page 12, section E.1.a.). Clearly, the appellant is conceding that Hanson anticipates embodiments of independent claims 1, 8 and 17, because these claims are not limited to acetate counterions. Additionally, these compositions are not indicated as structurally "comprising acetate." Acetate is merely part of the process of making. As for independent claims 26 and 28, the Office has provided teachings of Hanson in the anticipation rejection above (and Response to Argument Section D.1.b), which demonstrate that acetate can be introduced as a counterion, in the form of a chaotropic salt. When acetate chaotropic salts are introduced into the mixture of DNA and polycation, the acetate ion is a counterion to the polycation. Regarding Section E.1.b, see Response to Arguments, section D.1.b.

The appellant further argues that Hanson does not explicitly teach the same product as claimed (Brief, page 13, Section E.2). The appellant further states, "While indeed both Hanson and the subject application describe compositions that are heterogeneous, the subject application's composition has a component that is not present or taught in the Hanson composition. Hanson does not teach a complex which

is rod-shaped, 10-20 nm diameter, and contains a condensed nucleic acid." (Brief, page 13, section E.2). Contrary to the appellant's suggestion, Hanson et al. teach "non-naturally occurring soluble compacted complexes of a nucleic acid and a carrier molecule" (column 66, lines 36-37). Hanson teach "electron microscopic results have been indicated as follows: the association of the polycation with the DNA results in…the structure resulting from the condensation are rod-like relaxed toroids of increased size (relaxed)" (col.62, lines 51-54). Hanson et al. further teach a relaxed complex having "rod-like fibers (usually 10-20 times the diameter of naked DNA fiber, i.e., usually 10-20 nm thick, and longer than 60 nm) of DNA and branched toroidal structures of increasing size" (col. 58, middle of page). Clearly, Hanson teaches compacted complexes of DNA and polycation, which have a rod shape and are 10-20 nm thick. The Office interprets these teachings as satisfying the structural limitations of the instant claims.

The appellant argues that Hanson's toroids do not spontaneously form condensed rods (Brief, page 14, Section E.3). Brief, page 11, section D.2 describes the appellant's characterization of the teachings of Martin. The appellant discusses Martin to argue that the conditions of making compacted complexes of DNA-poly-L-lysine are substantially important to the patentability of the instant claims. The art is replete with examples of compacted complexes of DNA-poly-L-lysine; many of them have been characterized as having both toroid and rod-shaped morphologies. In part, the prosecution of the instant application has come to the point of Appeal because of a disagreement between the Office and the Applicant over the subject of the rod-shaped complexes. The Office introduced the Martin reference during the course of prosecution

in an attempt to demonstrate the art's emerging understanding of the relationship between the toroid structures and the rod-shaped structures. Martin attempts to understand the forces that generate the two forms (i.e., toroid and rod-shaped) that are common in formulations of compacted complexes of DNA-poly-L-lysine.

The appellant asserts (Brief, page 14, lines 20-23) that the different conditions used by Martin and Hanson generate structurally different compacted complexes of DNA-poly-L-lysine. The appellant characterizes the teachings of Hanson as producing aggregates (Brief, page 14, lines 23), which are not taught by Martin. It is true that Hanson describes conditions where DNA-PLL can aggregate. A large portion of Hanson is devoted to the study of the various parameters which result in compacted complexes of DNA-poly-L-lysine. In the course of their studies, Hanson expands the ranges of salt concentration and polylysine concentration to the point where aggregation occurs, in order to study the ranges where compacted complexes of DNA-poly-L-lysine can form. The conditions of Martin do not form aggregates because Martin uses conditions that are known to form condensates.

The appellant seems particularly concerned about the Martin's use of mica as an atomic force microscopy (AFM) imaging platform substrate upon which the DNA-PLL condenses. Martin performed Atomic Force Microscopy using aqueous conditions, in order to examine the real-time conformational changes of DNA-polymer condensates because this eliminates some of the structural artifacts produced during sample processing for transmission electron microscopy where molecules are fixed and unable to move (page 106, col.2, 2nd parag.). Martin seems to indicate that the mica substrate

has not restrained the complexes from altering their various shapes as he conjectures normally occurs in methods of making DNA-polylysine in bulk solution: "[i]mportantly, because immobilisation in this study has been achieved simply on bare mica without substrate modification or the addition of multivalent cations, conformational change has not been induced by immobilisation chemicals" (page 109, col.1). In other words, Martin is eliminating variables from the conditions of his experiments which might alter the conditions of DNA-polylysine condensation, thereby permitting real-time visualization of DNA-polylysine conformational changes. Therefore, the Office is not convinced that the methods of Hanson and Martin would generate substantially different compacted complexes of DNA-poly-L-lysine.

Using atomic force microscopy, sequential images provide real-time evidence that the rod-shaped complexes of DNA-polylysine are related to the toroid shaped complexes (section 3.3, page 111). Specifically, Martin states: "When regarding cation-induced DNA condensation an unresolved issue is whether rods are intermediates of toroidal formation or toroids intermediates of rod formation, or indeed whether they are distinct of one another." (page 111, col.1, 2nd parag). Martin concludes "[w]e believe we are observing a stage of condensate formation where ring and rod-like structures exist dynamically, having the ability to reversibly equilibrate between structures" (page 111, col.1, parag.3). Therefore, absence evidence to the contrary, the presence of rod-shaped condensed DNA complexes in a composition of compacted complexes of DNA-poly-L-lysine is inherent.

Based upon the arguments presented by the appellant and the teachings of Hanson, the Office concludes that the claimed compositions are anticipated by Hanson.

Obviousness over Hanson, Park & Schacht

The appellant has not provided specific argument against this combination of references. Rather, the appellant has reiterated her assertion that "Hanson does not teach a method of making which utilizes a polycation with an acetate counterion, nor does Hanson teach complexes that are unaggregated, rod-shaped, 10-20 nm in diameter, have condensed nucleic acid, and are colloidally stable in normal saline" (Brief, page 17, 1st parag.). The instant claims are product-by-process claims; no pending claims are purely method claims. The Office has described in the anticipation rejection, that Hanson teaches the claimed structural properties of the anticipated claims. The claims rejected under 35 USC 103 as obvious over Hanson, Park & Schacht, require further limitations not taught by Hanson, but which are taught by Park & Schacht. The appellant has summarized these teachings at Brief, page 17, lines 6-9. As the appellant has not disputed the obviousness of compositions of compacted complexes of DNA-poly-L-lysine that also include PEG and disulfide cysteine linkages, the Office interprets this to mean that the appellant accepts that these polycation modifications are obvious.

Obviousness over Hanson, Park & Mao

The appellant has not provided specific argument against this combination of references. Rather, the appellant has reiterated her assertion that "Hanson does not teach a method of making which utilizes a polycation with an acetate counterion, nor does Hanson teach complexes that are unaggregated, rod-shaped, 10-20 nm in diameter, have condensed nucleic acid, and are colloidally stable in normal saline" (Brief, page 17, 1st parag.). The instant claims are product-by-process claims; no pending claims are purely method claims. The Office has described in the anticipation rejection, that Hanson teaches the claimed structural properties of the anticipated claims. The claims rejected under 35 USC 103 as obvious over Hanson, Park & Mao, require further limitations not taught by Hanson, but which are taught by Park & Mao. The appellant has summarized these teachings at Brief, page 17, lines 6-7 and 10. As the appellant has not disputed the obviousness of compositions of compacted complexes of DNA-poly-L-lysine that have been lyophilized and resuspended, the Office interprets this to mean that the appellant accepts that these forms of compacted complexes are obvious.

Obviousness over Hanson, Park, Schacht & Kwoh

The appellant has made several arguments against this combination of references. In particular, the appellant has made numerous arguments regarding the teachings of Kwoh.

The appellant has reiterated her assertion that "Hanson does not teach a method of making which utilizes a polycation with an acetate counterion, nor does Hanson teach complexes that are unaggregated, rod-shaped, 10-20 nm in diameter, have condensed nucleic acid, and are colloidally stable in normal saline" (Brief, page 17, 1st parag.). The instant claims are product-by-process claims; no pending claims are purely method claims. The Office has described in the anticipation rejection, that Hanson teaches the claimed structural properties of the anticipated claims. The claims rejected under 35 USC 103 as obvious over Hanson, Park, Schacht & Kwoh, require further limitations not taught by Hanson, but which are taught by Park, Schacht & Kwoh. The appellant has not disputed the obviousness of compositions of compacted complexes of DNA-poly-L-lysine that also include PEG (as taught by Schacht) and disulfide cysteine linkages (as suggested by Park). The Office interprets this to mean that the appellant accepts that these polycation modifications are obvious. Therefore, the Office will focus primarily on the arguments against Kwoh.

The appellant has asserted that the condensed nucleic acid-polylysine complexes of Kwoh are not colloidally stable in normal saline (Brief, page 17, last parag). Contrary to the appellant's assertion, Kwoh et al. teach condensed nucleic acid-polylysine complexes are colloidally stable in normal saline. Kwoh et al. teach "[t]he

size and stability of polyplexes made with the different sizes of PLL have been characterized both in water and at physiological ionic strength" (page 173, col.1, parag.1). Kwoh et al. teach polyplex aggregation can be eliminated by incorporation of minimal amounts of PEG. The PLL10K-PEG5 (1:2) polyplexes were more stable over time in physiological saline than PLL10K or AP26K polyplexes." (page 187, col.2, parag.2). Kwoh et al. teach "solubility in physiological saline was slightly greater for AP26K polyplexes than for PLL polyplexes if examined at time ≤ 30 minutes" (page 187, col.1, parag.1). While Kwoh et al. teach that PLL polyplexes are less soluble in physiological saline than other condensed DNA complexes, this teaching by Kwoh, does not indicate that the PLL polyplexes are insoluble or not colloidally stable in physiologically saline. The claims do not provide any further limitations than "said complexes are colloidally stable in normal saline." Kwoh at page 187, col.1, lines 13-15, indicate that PLL polyplexes have some degree of colloidal stability in normal saline. Additionally, Kwoh emphasizes that the addition of PEG to the DNA-poly-L-lysine complexes eliminates aggregation and is stable in physiological saline. Although the appellant argues that Kwoh teaches away from the claimed invention (Brief, page 18, lines 17-18) because "Kwoh teaches complexes that are colloidally unstable" (Brief, page 18, line 16), the Office finds the appellant's argument unpersuasive because Kwoh clearly states that DNA-poly-L-lysine-PEG complexes are stable in physiological (normal) saline (page 187, col.2, lines 34-37). Furthermore, Kwoh suggests that DNA-poly-L-lysine complexes also have some degree of stability in physiological saline (page 187, col.1, lines 13-15), so they cannot be called unstable.

The appellant also argues that none of the secondary references demonstrate the use of acetate as a counterion. The Office agrees that none of the secondary references demonstrate the use of acetate as a counterion. However, Hanson et al. teach use of acetate ion in the preparation of condensed DNA-poly-L-lysine complexes, suggesting that acetate is a counterion during mixing.

Accordingly, the Office finds the appellant's arguments unpersuasive.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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